

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS : Tom W. Muir *et al*
SERIAL NO. : UNASSIGNED EXAMINER : Unknown
FILED : HEREWITH ART UNIT : 1654
FOR : NOVEL STAPHYLOCOCCUS PEPTIDES FOR
BACTERIAL INTERFERENCE

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

Sir:

Prior to calculating the filing fees for the above identified application, please amend
the above-identified Application as follows:

IN THE SPECIFICATION:

On page 1, line 10, please amend as follows:

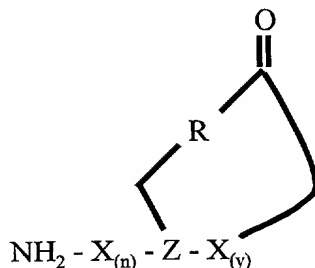
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CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a Continuation of co-pending application Serial No. 09/339,511,
filed June 24, 1999, which, in turn, claims priority under 35 U.S.C. § 119(e) from Provisional
Application Serial No. 60/090,402, filed June 24, 1998. The disclosures of both applications
are incorporated herein by reference in their entirety. --

On page 4, please amend the paragraph extending from lines 2 - 8 as follows:

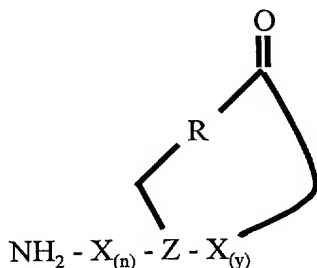
-- The present invention provides a cyclic peptide comprising the structure:



wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10. The invention also contemplates a peptide composition comprising the provided cyclic peptide and a carrier. --

On page 8, please amend the paragraph extending from lines 2 - 6 as follows:

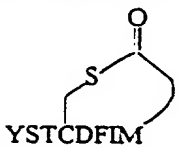
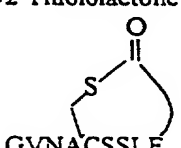
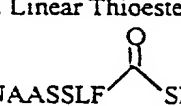
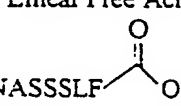
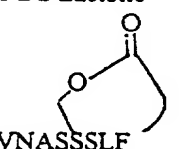
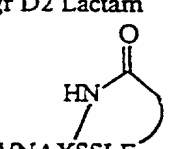
-- The present invention provides a cyclic peptide comprising the structure:



wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10. --

On Page 16, line 21, after "(Table 1)." Please insert Table 1 as follows:

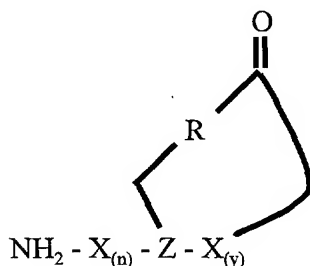
TABLE I
BIOLOGICAL ACTIVITY OF SYNTHETIC AgrD PEPTIDES

PEPTIDE	ED ₅₀ Activation (nM)			IC ₅₀ Inhibition (nM)		
	<i>S. aureus</i> Group			<i>S. aureus</i> Group		
	I	II	III	I	II	III
Agr D1 Thiolactone  YSTCDFIM	10.2	No Activation	No Activation	No Inhibition	2.9	3.2
Agr D2 Thiololactone  GVNACSSLF	No Activation	3.6	No Activation	3.4	No Inhibition	3.1
Agr D2 Linear Thioester  GVNAASSLF-SR	No Activation	No Activation	No Activation	No Inhibition	No Inhibition	No Inhibition
Agr D2 Linear Free Acid  GVNASSSLF-OH	No Activation	No Activation	No Activation	No Inhibition	No Inhibition	No Inhibition
Agr D2 Lactone  GVNASSSLF	No Activation	No Activation	No Activation	7.9	No Inhibition	n/d
Agr D2 Lactam  GVNAXSSLF	No Activation	No Activation	No Activation	0.21	No Inhibition	n/d

On Page 32, please replace the Abstract with the following:

--ABSTRACT OF THE DISCLOSURE

The present invention provides a cyclic peptide comprising the structure:

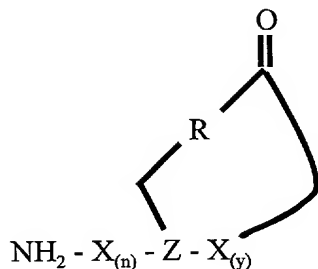


wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10. The present invention also provides a cyclic peptide comprising the amino acid sequence of NH₂-X_(n)-Z-X_(y)-COOH and a cyclic bond between the Z residue and COOH other than a thioester bond, wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, n is 0 to 10 and y is 1 to 10. Methods of preparation including a cyclization protocol, and methods of use of the cyclic peptides of the invention are also disclosed. --

IN THE CLAIMS:

Please amend the claims as follows:

1. (Amended) A cyclic peptide comprising the structure:



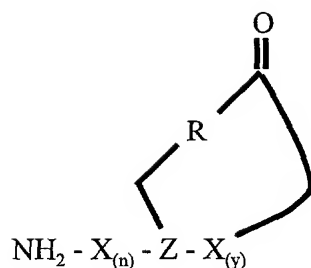
wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10,

wherein the cyclic peptide is capable of inhibiting the *agr* response.

2. Amended) A cyclic peptide comprising the amino acid sequence of NH₂-X_(n)-Z-X_(y)-COOH and a cyclic bond between the Z residue and COOH other than a thioester bond, wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, n is 0 to 10 and y is 1 to 10,

wherein the cyclic peptide is capable of inhibiting the *agr* response.

17. (Amended) A method for treating *S. aureus* infection in a subject comprising administering to the subject an amount of a cyclic peptide effective to treat the infection, said cyclic peptide comprising the structure:



wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10.

18. (Amended) A method for treating *S. aureus* infection in a subject comprising administering to the subject an amount of a cyclic peptide effective to treat the infection, said cyclic peptide comprising the amino acid sequence of $\text{NH}_2\text{-X}_{(n)}\text{-Z-X}_{(y)}\text{-COOH}$ and a cyclic bond between the Z residue and COOH other than a thioester bond, wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, n is 0 to 10 and y is 1 to 10.

Please cancel Claims 3-16 and 19-24 without prejudice.

Please add the following new claims:

– 25. The method of claim 17, wherein Z has a side chain comprising oxygen, nitrogen or carbon.

26. The method of claim 18, wherein Z has a side chain comprising oxygen, nitrogen or carbon.

27. The method of claim 18, wherein the cyclic bond is a lactam or lactone bond.
28. The method of claim 17, wherein the cyclic peptide is capable of inhibiting the *agr* response.
29. The method of claim 18, wherein the cyclic peptide is capable of inhibiting the *agr* response.
30. The method of claim 17, wherein y is 4.
31. The method of claim 18, wherein y is 4.
32. The method of claim 30, wherein the peptide is selected from the group of peptides having an amino acid sequence that comprises G-V-N-A-X-S-S-L-F (Seq.ID No.:1), G-A-N-A-X-S-S-L-F (Seq.ID No.:2), A-V-A-N-X-S-S-L-F (Seq.ID No.:4), G-V-N-A-X-A-S-L-F (Seq.ID No.:5), G-V-N-A-X-S-A-L-F (Seq.ID No.:6), G-V-N-A-X-S-S-A-F (Seq.ID No.:7) and X-S-S-L-F (Seq.ID No. 8).
33. The method of claim 31, wherein the peptide is selected from the group of peptides having an amino acid sequence that comprises G-V-N-A-X-S-S-L-F (Seq.ID No.:1), G-A-N-A-X-S-S-L-F (Seq.ID No.:2), G-V-A-A-X-S-S-L-F (Seq.ID No.:3), A-V-A-N-X-S-S-L-F (Seq.ID No.:4), G-V-N-A-X-A-S-L-F (Seq.ID No.:5), G-V-N-A-X-S-A-L-F (Seq.ID No.:6), G-V-N-A-X-S-S-A-F (Seq.ID No.:7) and X-S-S-L-F (Seq.ID No. 8).
34. The method of claim 17, wherein a composition is administered and said composition comprises said peptide and a carrier.
35. The method of claim 18, wherein a composition is administered and said composition comprises said peptide and a carrier.

36. The method of claim 17, wherein a pharmaceutical composition is administered and said pharmaceutical composition comprises said peptide and a pharmaceutically acceptable carrier.

37. The method of claim 18, wherein a pharmaceutical composition is administered and said pharmaceutical composition comprises said peptide and a pharmaceutically acceptable carrier.

38. The pharmaceutical composition of claim 36, wherein the carrier is selected from the group consisting of a diluent, an aerosol, a topical carrier, an aqueous solution, a nonaqueous solution, and a solid carrier.

39. The pharmaceutical composition of claim 37, wherein the carrier is selected from the group consisting of a diluent, an aerosol, a topical carrier, an aqueous solution, a nonaqueous solution, and a solid carrier. --

REMARKS

The above amendments to the Specification and Claims are being submitted concurrently with filing so as to assure that the file wrapper reflects the resolution of informalities that were noted and corrected in parent application Serial No. 09/339,511. Thus, the above amendments to the Specification and claims were submitted together with a response to a Restriction Requirement in the parent application, and were accepted. The following comments were placed on the record in the parent application with respect to such amendments, and are repeated below for completeness herein.

The above amendments to the specification and to Claim 1 to include the instance where R is sulfur, seek to correct an inadvertent omission in the general structural formula presented with respect to the cyclic peptides of the present invention. Particularly, a review of the examples herein and the specific exemplary peptides presented in SEQ. ID NOS. 1-8, all include sulfur as part thereof. Yet further, a review of the ligation strategy set forth in Figure 1A and described in Example 1, makes it clear that sulfur was intended as a

substituent in the peptide structure.

As will be noted, the amendment to the structural formula occurs at all locations where the formula is presented, including three locations in the Specification and in Claim 1. As this amendment is not believed to raise new matter, entry and favor consideration thereof are requested.

Also, Applicants submit herewith Table 1 for inclusion on page 16 of the application as filed, in correspondence with its inclusion in prior filed Priority Application Serial No. 60/090,402, which disclosure was incorporated herein in its entirety by reference as per the statement to this effect appearing on page 1, lines 11-13 of the application as filed. In addition, there is abundant reference to the content and disclosure of Table 1 appearing throughout Example 1 (see page 16, lines 5, 11, 15 and 21) as well as corresponding reference in Example 2 (page 17, line 15) and Example 3 (page 18, line 10). Accordingly, Applicants submit that sufficient basis and disclosure corresponding to the contents of Table 1 is amply set forth in the application as filed herein, so that in combination with the incorporation by reference of prior filed Provisional Application Serial No. 60/090,402, sufficient basis and justification exists for the entry of Table 1 herein without the consideration that new matter results thereby. Accordingly, entry of Table 1 is believed to be in order, and is hereby requested.

The above Preliminary Amendment is also submitted to provide a more comprehensive set of claims for the methods of treatment using the cyclic peptides of the present invention as set forth in original claims 17 and 18. In particular, Claims 17 and 18 have been revised to incorporate the limitations of original Claims 1 and 2 with respect to the cyclic peptides, and new Claims 25-39 have been added to cover the variations on the peptides, and the respective recitations as to compositions that comprise the respective peptides. As the claims in question correspond to original claims 3-16, the insertion of the claims herein is not believed to constitute new matter.

Lastly, Claims 5 and 6 that were canceled during the prosecution of the parent application are introduced herein in independent form as amended versions of original Claims 1 and 2. Applicants wish to reiterate herein that the cancellation of Claims 5 and 6 from parent application Serial No. 09/339,511 was purely for the purpose of expediting the

issuance of the claims deemed allowable, and without prejudice or forfeiture of the subject matter thereof. Applicants believe that amended Claims 1 and 2 are patentable and entitled to favorable consideration, and such action is accordingly requested.

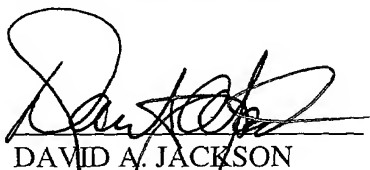
In keeping with the procedures in place for the submission of amendments, an attachment to this response includes a version of the amendments made above showing the changes as marked up.

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PATENT
600-1-231N CON

Accordingly favorable consideration and entry of the above amendments, and an early and favorable action on the merits, are courteously solicited.

Respectfully submitted,



DAVID A. JACKSON
Attorney for Applicant(s)
Registration No. 26,742

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(201) 487-5800

ENCLOSURE: Marked-Up Version of Amendments

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS : Tom W. Muir *et al*
SERIAL NO. : UNASSIGNED EXAMINER : Unknown
FILED : HEREWITH ART UNIT : 1654
FOR : NOVEL STAPHYLOCOCCUS PEPTIDES FOR
BACTERIAL INTERFERENCE

PRELIMINARY AMENDMENT

VERSION OF AMENDMENTS SHOWING MARK-UPS OF SPECIFICATION AND
CLAIMS

IN THE SPECIFICATION:

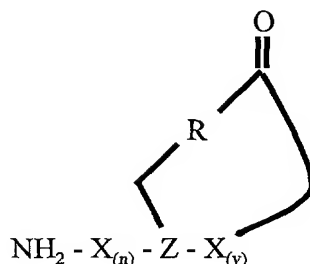
On page 1, line 10, please amend as follows:

-- CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a Continuation of co-pending application Serial No. 09/339,511,
filed June 24, 1999, which, in turn, claims priority under 35 U.S.C. § 119(e) from Provisional
Application Serial No. 60/090,402, filed June 24, 1998. The [, the] disclosures of both
applications are [which is] incorporated herein by reference in [its] their entirety. --

On page 4, please amend the paragraph extending from lines 2 - 8 as follows:

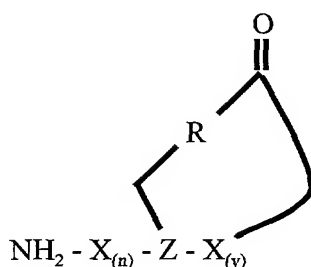
-- The present invention provides a cyclic peptide comprising the structure:



wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10. The invention also contemplates a peptide composition comprising the provided cyclic peptide and a carrier. --

On page 8, please amend the paragraph extending from lines 2 - 6 as follows:

-- The present invention provides a cyclic peptide comprising the structure:



wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10. --

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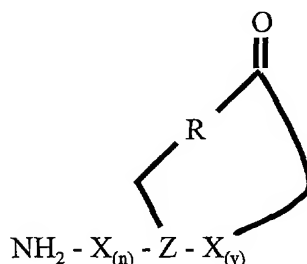
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On Page 32, please replace the Abstract with the following:

--ABSTRACT OF THE DISCLOSURE

The present invention provides a cyclic peptide comprising the structure:

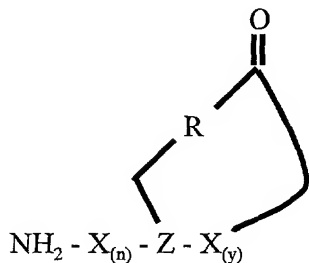


wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10. The present invention also provides a cyclic peptide comprising the amino acid sequence of NH₂-X_(n)-Z-X_(y)-COOH and a cyclic bond between the Z residue and COOH other than a thioester bond, wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, n is 0 to 10 and y is 1 to 10. Methods of preparation including a cyclization protocol, and methods of use of the cyclic peptides of the invention are also disclosed. --

IN THE CLAIMS:

Please amend the claims as follows:

1. (Amended) A cyclic peptide comprising the structure:



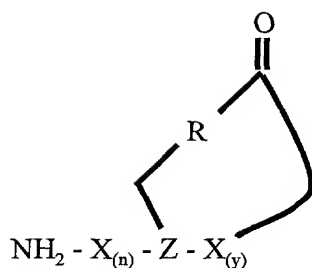
wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10,

wherein the cyclic peptide is capable of inhibiting the *agr* response.

2. (Amended) A cyclic peptide comprising the amino acid sequence of $\text{NH}_2 - \text{X}_{(n)} - \text{Z} - \text{X}_{(y)} - \text{COOH}$ and a cyclic bond between the Z residue and COOH other than a thioester bond, wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, n is 0 to 10 and y is 1 to 10,

wherein the cyclic peptide is capable of inhibiting the *agr* response.

17. (Amended) A method for treating *S. aureus* infection in a subject comprising administering to the subject an amount of a cyclic peptide [the pharmaceutical composition of claim 15] effective to treat the infection, said cyclic peptide comprising the structure:



wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10.

18. (Amended) A method for treating *S. aureus* infection in a subject comprising administering to the subject an amount of a cyclic peptide [the pharmaceutical composition of claim 16] effective to treat the infection, said cyclic peptide comprising the amino acid sequence of NH₂-X_(n)-Z-X_(y)-COOH and a cyclic bond between the Z residue and COOH other than a thioester bond, wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, n is 0 to 10 and y is 1 to 10.

Please cancel Claims 3-16 and 19-24 without prejudice.

Please add the following new claims:

– 25. The method of claim 17, wherein Z has a side chain comprising oxygen, nitrogen or carbon.

26. The method of claim 18, wherein Z has a side chain comprising oxygen, nitrogen or carbon.

27. The method of claim 18, wherein the cyclic bond is a lactam or lactone bond.
28. The method of claim 17, wherein the cyclic peptide is capable of inhibiting the *agr* response.
29. The method of claim 18, wherein the cyclic peptide is capable of inhibiting the *agr* response.
30. The method of claim 17, wherein y is 4.
31. The method of claim 18, wherein y is 4.
32. The method of claim 30, wherein the peptide is selected from the group of peptides having an amino acid sequence that comprises G-V-N-A-X-S-S-L-F (Seq.ID No.:1), G-A-N-A-X-S-S-L-F (Seq.ID No.:2), G-V-A-A-X-S-S-L-F (Seq.ID No.:3), A-V-A-N-X-S-S-L-F (Seq.ID No.:4), G-V-N-A-X-A-S-L-F (Seq.ID No.:5), G-V-N-A-X-S-A-L-F (Seq.ID No.:6), G-V-N-A-X-S-S-A-F (Seq.ID No.:7) and X-S-S-L-F (Seq.ID No. 8).
33. The method of claim 31, wherein the peptide is selected from the group of peptides having an amino acid sequence that comprises G-V-N-A-X-S-S-L-F (Seq.ID No.:1), G-A-N-A-X-S-S-L-F (Seq.ID No.:2), G-V-A-A-X-S-S-L-F (Seq.ID No.:3), A-V-A-N-X-S-S-L-F (Seq.ID No.:4), G-V-N-A-X-A-S-L-F (Seq.ID No.:5), G-V-N-A-X-S-A-L-F (Seq.ID No.:6), G-V-N-A-X-S-S-A-F (Seq.ID No.:7) and X-S-S-L-F (Seq.ID No. 8).
34. The method of claim 17, wherein a composition is administered and said composition comprises said peptide and a carrier.
35. The method of claim 18, wherein a composition is administered and said composition comprises said peptide and a carrier.

36. The method of claim 17, wherein a pharmaceutical composition is administered and said pharmaceutical composition comprises said peptide and a pharmaceutically acceptable carrier.

37. The method of claim 18, wherein a pharmaceutical composition is administered and said pharmaceutical composition comprises said peptide and a pharmaceutically acceptable carrier.

38. The pharmaceutical composition of claim 36, wherein the carrier is selected from the group consisting of a diluent, an aerosol, a topical carrier, an aqueous solution, a nonaqueous solution, and a solid carrier.

39. The pharmaceutical composition of claim 37, wherein the carrier is selected from the group consisting of a diluent, an aerosol, a topical carrier, an aqueous solution, a nonaqueous solution, and a solid carrier. --